IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF ARKANSAS
WESTERN DIVISION

In re:	**MDL Docket No. 4:03CV1507 WRW**
PREMPRO PRODUCTS LIABILITY LITIGATION	***Reeves v. Wyeth*, 4:05-cv-00163-WRW** ***Rush v. Wyeth*, 4:05-cv-00497-WRW**

REPLY IN SUPPORT OF WYETH'S
MOTION TO EXCLUDE EXPERT TESTIMONY OF
DRS. KLIMBERG AND WALDRON AS TO SPECIFIC CAUSATION

Most women who develop breast cancer have never taken hormone therapy, and most women who have taken hormone therapy never develop breast cancer. At present, medical science cannot tell us why breast cancer afflicts some women, but not others.

The Court need not decide now whether it is ever possible, in any case, for an expert to say, "I know what caused this woman's breast cancer." The issue before the Court is only whether Drs. Klimberg and Waldron can testify that hormone therapy caused ***Ms. Reeves'*** and ***Ms. Rush's*** breast cancers, and that question has four answers:

- *First*, Dr. Waldron concedes that hormone therapy did not cause Plaintiffs' breast cancers, if "cause" is used in the conventional sense of "initiate" cancerous cells. Moreover, Dr. Waldron's own formula for calculating the age of a tumor demonstrates that Plaintiffs' breast tumors were present ***before*** they started hormone therapy.

- *Second*, even accepting the experts' theory that breast density is associated with breast cancer, Plaintiffs' mammogram films reveal that they did not experience the kind of breast density changes "promoted" by hormone therapy, as Dr. Klimberg admits.

- *Third*, Drs. Klimberg and Waldron cannot compensate for the lack of objective evidence that hormone therapy initiated or promoted Plaintiffs' breast cancers by relying on differential diagnosis, a diagnostic method that, as Dr. Westbrook has explained, is not used to determine the specific cause of breast cancer. It cannot be used for that purpose, because, even if all but one of the known risk factors can been ruled out, the "X" factor—

the ***unknown*** factor that "accounts" for breast cancer in most women—can never be ruled out.

- *Fourth*, Drs. Klimberg and Waldron, who are not epidemiologists, cannot rely on cherry-picked epidemiological studies. Like differential diagnosis, such studies are not—and cannot here be—used to prove specific causation, as their own expert admits.

I. HORMONE THERAPY DOES NOT—AND DID NOT—*INITIATE* PLAINTIFFS' BREAST CANCERS.

Medical science has identified some of the "risk factors" for breast cancer—*i.e.*, factors associated with an increased incidence of breast cancer, but, "[e]ven when a woman with breast cancer has a risk factor, ***there is no way to prove that it actually caused her cancer***."[1] It is not even clear, from Plaintiffs' Opposition, whether they contend that hormone therapy really ***caused*** (*i.e.*, initiated) their breast cancers or merely ***promoted*** the growth of pre-existing tumors. What is clear, according to Dr. Waldron's testimony, is that "the notion that hormone replacement therapy initiates a new tumor is not generally accepted in the scientific community" and that "relative risk associations relate to promotion and potentiation," not "initiation."[2] In fact, Dr. Waldron testified that "hormone therapy did not initiate Ms. Reeves' tumor, but instead played some role in the speed with which it developed."[3] Moreover, the Opposition's assertion that Ms. Reeves and Ms. Rush "began taking CMHT before they developed cancer, not after"[4]—

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1 American Cancer Society, *Breast Cancer, What Are the Risk Factors for Breast Cancer?* (2005) (App., Ex. 41) (emphasis added); *see also* Westbrook Aff. (App., Ex. 36) ¶ 3 ("[A]t the present time, there is no way to determine if a particular risk factor . . . causes the development of a specific woman's breast cancer.").

2 Waldron Dep. (excerpts attached as Ex. 1) at 350:1-12.

3 *Id*. at 375:12-22. Dr. Klimberg never stated that hormone therapy initiated Plaintiffs' tumors.

4 Plaintiffs' Opposition to Defendants' Motion to Exclude Expert Testimony of Drs. Klimberg and Waldron as to Specific Causation (June 29, 2006) [*Reeves* Docket No. 142; *Rush* Docket No. 211] ("Pl. Opp.") at 14.

for which the Opposition cites no supporting evidence—is inconsistent with Dr. Waldron's testimony that the average tumor doubles in size every 150 days.[5] According to Dr. Waldron's own calculation, Ms. Rush's tumor, which was approximately 0.4 cm, must have been growing for more than ten years[6]—starting two years or more ***before*** she first used hormone therapy. And, Ms. Reeves' tumor, which was 1.5 cm (about four times larger than Ms. Rush's tumor), must have developed even earlier.[7] At the very least, therefore, ***the Court should exclude any testimony that hormone therapy caused (i.e., initiated) Plaintiffs' breast cancers***.[8]

II. BY PLAINTIFFS' OWN ANALYSIS, THE MAMMOGRAM FILMS—THE ONLY OBJECTIVE EVIDENCE—PROVE THAT HORMONE THERAPY DID NOT *PROMOTE* PLAINTIFFS' BREAST CANCERS.

Daubert insists that the expert's theory "fit" the case by being grounded in the case-specific facts; otherwise, it cannot "assist the trier of fact," as Rule 702 requires. Here, there is no objective evidence that hormone therapy caused (in the sense of "promoted") Plaintiffs' breast cancers. They were diagnosed with invasive ductal carcinoma, the most common type of

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[5] Waldron Dep. at 30:3-5.

[6] *Id.* at 31:17-32:15. Waldron's calculation likely understates the growth period for Ms. Rush's tumor because his calculation was based on a linear, average growth rate; as Waldron conceded, however, Ms. Rush had a particularly slow growing tumor. *See id.* at 30:9-14.

[7] Dr. Klimberg has never testified that Ms. Reeves or Ms. Rush used hormone therapy before developing breast cancer. Generally, she advises her patients of a five-to-ten-year timeframe from initiation to detection. *See* Klimberg Dep. (excerpts attached as Ex. 2) at 113:2-22.

[8] Applying the same reasoning in the context of breast implant litigation, the court concluded that the plaintiff's expert's opinion that the plaintiff's breast cancer had been "induced after implantation" was "unreliable and inadmissible under *Daubert* and Fed. R. Evid. 702." *In re Silicone Breast Implant Prods. Liab. Litig.*, 318 F. Supp. 2d 879, 919 (C.D. Cal. 2004). Based on the plaintiff's expert's own assumptions about the average doubling time of a tumor and the objective evidence about the size of the plaintiff's tumor, the court calculated that the plaintiff's tumor must have developed (and began doubling) *before* she received her breast implants and, thus, that the implants could not have *caused* her breast cancer. *See id.* The Court should reach the same conclusion here and exclude any expert testimony by Drs. Klimberg and Waldron that hormone therapy *caused* (*i.e.*, initiated) Plaintiffs' breast cancers.

breast cancer in women, irrespective of prior hormone therapy use. As Plaintiffs concede, no signature or marker links their breast cancers to hormone therapy.[9] Nor does the fact that their tumors were hormone-receptor positive establish any hormone therapy link; Dr. Klimberg testified that women who take hormone therapy have both endogenous and exogenous hormones; that the two interact with hormone receptors in the "same way"; and that there is no way to "segregate out the effect of . . . endogenous hormones from the exogenous hormones."[10] Indeed, Plaintiffs have not identified any aspect of their tumors (*e.g.*, size, shape, type, location, pattern, cancer cell characteristics, or mitotic rate) to support their causal claims.

Plaintiffs' only argument—their purportedly "powerful evidence"—is that they allegedly "experienced maintained or increased breast density" after taking hormone therapy, so hormone therapy must have affected their breasts.[11] Nevermind that an effect on breast density is not tantamount to an effect on breast cancer; even if it were, Plaintiffs' argument is refuted by the objective evidence. Comparing Plaintiffs' mammogram films from before, during and after their use of hormone therapy shows ***no change*** in breast density.[12] Plaintiffs' own experts concur.

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[9] Pl. Opp. at 6-8.

[10] Klimberg Dep. at 509:15-510:11 ("There is no way to measure that.").

[11] Pl. Opp. at 15. Plaintiffs' suggestion that Dr. Klimberg used the Gail Model to determine that hormone therapy *caused* Plaintiffs' breast cancers is disingenuous, at best. *See id.* at 3. "The Gail Model was *not* designed to identify what caused a specific woman's breast cancer" and "has not been studied, tested, or validated for that purpose." Westbrook Aff. ¶ 10 (emphasis added). Moreover, the Gail Model could not possibly identify hormone therapy as a cause of breast cancer because, as Dr. Klimberg concedes, it does not even include the use of hormone therapy as a recognized risk factor, *see* Klimberg Dep. at 261:23-262:2; *see also* "About the Gail Model," www.cancer.gov/bcrisktool/about-tool.aspx (attached as Ex. 3).

[12] Affidavits of Dr. Steven E. Harms ("Harms Affs.") ¶ 2 (attached as Ex. 4). Plaintiffs' breast density did not increase when they were taking hormone therapy, and both women maintained the same level of density for years after they stopped taking hormone therapy. These findings constitute a double-barreled refutation of their experts' breast density theory as applied to Ms. Reeves and Ms. Rush.

Dismissing any changes in Plaintiffs' breast density as "minimal," Dr. Klimberg testified that, in reviewing Plaintiffs' mammogram films, she did not "see ***any*** change over time" in either woman's breast density.[13] Plaintiffs' "powerful evidence of drug effect" is pure fiction: the density of Plaintiffs' breast neither increased when they began taking hormone therapy nor decreased when they stopped, indicating that their breast density was unaffected by their hormone therapy use.[14]

III. DIFFERENTIAL DIAGNOSIS CANNOT DETERMINE THE SPECIFIC CAUSE OF PLAINTIFFS' BREAST CANCERS.

Wyeth does not take issue with Plaintiffs' recitation of the law on differential diagnosis, only with its applicability here.[15] When they go to the office each day, Drs. Klimberg and Waldron do not use differential diagnosis to determine the specific cause of their patients' breast cancers—a classic red flag under *Daubert*.[16] They have done so here only because Plaintiffs

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[13] Klimberg Dep. at 30:12-23 (Rush); 30:24-31:19 (Reeves); 222:17-223:13 (emphasis added).

[14] Pl. Opp. at 15.

[15] *See Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 591 (1993) ("[S]cientific validity for one purpose is not necessarily scientific validity for other, unrelated purposes.").

[16] A "very significant fact" that the Court must consider is "whether the experts are proposing to testify about matters growing naturally and directly out of research they have conducted independent of litigation, or whether they have developed their opinions expressly for purposes of testifying." *Daubert v. Merrell Dow Pharm., Inc.*, 43 F.3d 1311, 1317 (9th Cir. 1995). Dr. Klimberg diagnoses and treats breast cancer, but she does not routinely identify the specific cause of a particular patient's breast cancer. In fact, as Dr. Westbrook has explained: "It is generally accepted at the present time in medical and scientific communities, that . . . there is no way to determine what caused an individual woman's breast cancer." Westbrook Aff. ¶ 3. Similarly, Dr. Waldron examines tissue samples for breast cancer but does not customarily opine on the cause of that cancer. *See* Waldron Dep. at 318:22-319:1. In fact, Dr. Waldron conceded that he cannot even tell, from a breast cancer slide, whether a woman has ever taken hormone therapy. *See id.* at 341:2-7.

have paid them as much as $1,000 per hour to develop favorable causation opinions expressly for this litigation.[17]

Dr. Westbrook should know, and he has explained: "The method of differential diagnosis is a well accepted technique in medicine for ***diagnosing*** a particular medical condition. It is not generally used," as Drs. Klimberg and Waldron have done, to "determine the ***specific cause*** of a specific diagnosis" or, more specifically, "to attempt to determine the cause of a particular woman's breast cancer."[18]

Furthermore, differential diagnosis cannot be applied reliably in the context of breast cancer because ***most*** post-menopausal women who develop breast cancer have no identifiable risk factors other than being women over the age of 50—risk factors shared by both Plaintiffs at the time of their diagnoses. Again, as Dr. Westbrook has explained:

> While you may be able to rule out certain [risk factors] in an individual case, you can never rule out all of the known risk factors (such as age and gender) ***and we know that there are unknown risk factors, so, by definition those could not be ruled out***.[19]

The inability to rule out certain risk factors in post-menopausal women, like Plaintiffs, means that differential diagnosis—a process premised on identifying the entire universe of potential risk factors and then whittling down alternative explanations until only the most likely remains—cannot be used to single out the specific cause of a woman's breast cancer.

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[17] Klimberg Rep. (App., Ex. 21) at 2.

[18] Westbrook Aff. ¶ 11 (emphasis added). While *Turner v. Iowa Fire Equipment Co.*, 229 F.3d 1202, 1208 (8th Cir. 2000), provides the "judicial" definition of differential diagnosis, the real world of medicine understands differential diagnosis as about just that—*diagnosis* of disease, not determination of its cause, *see* Dorland's Medical Dictionary at 369 (26th ed. 1981) ("the determination of which one of two or more diseases or conditions a patient is suffering from, by systematically comparing and contrasting their clinical findings").

[19] Westbrook Aff. ¶ 9 (emphasis added).

Drs. Klimberg and Waldron have not even systematically ruled out Plaintiffs' known risk factors. For example, they offer no rationale for excluding age as a risk factor—one that, standing alone, placed both Plaintiffs at "an increased risk."[20] They pay lip service to other serious risk factors, including obesity and nulliparity in Ms. Rush's case.[21] "An expert opinion that fails to consider the relevant facts of the case is fundamentally unsupported" and so "can offer no assistance to the jury" and "must be excluded."[22] Here, differential diagnosis has not been wielded as a rigorous scientific method but waved like a magic wand to make a predetermined (yet speculative) conclusion pop from Plaintiffs' hat.

IV. EPIDEMIOLOGICAL STUDIES CANNOT ESTABLISH THAT HORMONE THERAPY WAS THE SPECIFIC CAUSE OF PLAINTIFFS' BREAST CANCERS.

Nor can Drs. Klimberg and Waldron fall back on epidemiological studies to establish specific causation for two reasons, both of which rest on the simple premise that Plaintiffs cannot talk out of both sides of their mouths. First, Dr. Graham Colditz, Plaintiffs' very own epidemiological expert, has testified that epidemiological studies cannot prove that hormone therapy actually caused any individual woman's breast cancer, including Plaintiffs' breast

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[20] Klimberg Dep. at 201:8-202:1; *see also* McPherson Dep. (App., Ex. 24) at 325:20-326:20 (aging alone increases women's breast cancer risk by 1000%).

[21] Dr. Klimberg justified having ignored obesity as a risk factor on the ground that many women are obese. *See* Klimberg Dep. at 499:4-8. That logic, of course, would permit ignoring the risk of alcohol consumption in automobile accidents because many people drink and drive. Plaintiffs' suggestion that Dr. Klimberg's oversight was harmless because obesity is only a "modest risk factor," Pl. Opp. at 4 n.7, is remarkable, because Dr. Waldron testified that the relative risk of breast cancer from obesity is 1.5-2.0, *see* Waldron Dep. 61:9-15, *greater than that from hormone therapy (1.24), according to the WHI study*.

[22] *Neb. Plastics, Inc. v. Holland Colors Ams., Inc.*, 408 F.3d 410, 416 (8th Cir. 2005); *see also Nelson v. Am. Home Prods. Corp.*, 92 F. Supp. 2d 954, 970 (W.D. Mo. 2000).

cancers.[23] Second, the WHI study, which Plaintiffs called the "gold standard" and which their other epidemiological expert, Dr. David Sackett, has testified trumps the other studies they now cite,[24] reported a relative breast cancer risk from hormone therapy of only 1.24, well short of a doubling of the risk.

The Opposition has nothing to say about Dr. Colditz's unqualified statement, which constitutes a judicial admission by Plaintiffs.[25] Now ignoring WHI (because it does not suit their litigation purposes), Plaintiffs claim to have found 15 studies showing a doubling of the risk.[26] In reality, they have cherry-picked these 15 studies from the dozens that show a relative risk of less than 2.0 (many showing no effect or even a decreased breast cancer risk from hormone therapy),[27] including WHI and the meta-analysis conducted by Plaintiffs' own epidemiological expert, Dr. Colditz.[28] Notably, even the authors of Plaintiffs' studies do not identify any criteria

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[23] Colditz Dep. (App., Ex. 7) at 25:13-14; 37:16-18; *see id.* at 129:20-130:9; *see also* Westbrook Aff. ¶ 8.

[24] Sackett Dep. (excerpts attached as Ex. 5) at 136:2-136:4 ("[T]he Women's Health Initiative trumps the observational studies.").

[25] *See Postscript Enters. v. City of Bridgeton*, 905 F.2d 223, 227-28 (8th Cir. 1990); *Carson v. Pierce*, 726 F.2d 411, 411 (8th Cir. 1984); *EF Operating Corp. v. Am. Bldgs.*, 993 F.2d 1046, 1050 (3d Cir. 1993); *In re Stephenson*, 205 B.R. 52, 55 n.2 (Bankr. E.D. Pa. 1997) ("Counsel's unequivocal statements may, nevertheless, be given the effect of judicial admissions.").

[26] The studies cited by Plaintiffs in their Appendices are primarily from Europe, particularly Scandinavia (10 of the 15 studies are from Europe, and 9 from Scandinavia specifically), where the types of estrogen and progestin used are different and more strongly associated with breast cancer than those used in WHI and prescribed to Ms. Reeves and Ms. Rush. None of these studies appear to have looked at the same drug that was prescribed to Ms. Reeves and Ms. Rush. In addition, 11 of the 15 studies examined non-U.S. populations.

[27] Cherry-picking data from epidemiological studies is a hallmark of unreliable methodology. *See, e.g., Caraker v. Sandoz Pharm. Corp.*, 172 F. Supp. 2d 1046, 1049 (S.D. Ill. 2001).

[28] Graham A. Colditz et al., *Hormone Replacement Therapy and Risk of Breast Cancer: Results from Epidemiologic Studies,* Am. J. Obstetrics & Gynecology (1993) 168:1473-80; *see also*

that a practitioner could use to determine that hormone therapy (and not some other factor) caused a particular woman's breast cancer.

Illustrative of the misleading manner in which Plaintiffs employ even this small minority of studies is Plaintiffs' claim that, in the Rosenberg study, "women exposed to the ***same dose*** of CMHT" had a 2.3 fold increased risk of breast cancer.[29] That claim is false: the hormone therapy used in the Rosenberg study (i) had 2 milligrams of estradiol (a synthetic estrogen) compared to .625 milligrams of conjugated equine estrogen in Prempro and (ii) a testosterone-derived progestin compared to the medroxyprogesterone acetate used in Prempro. The study's authors specifically called attention to the differences between the form of hormone therapy studied and the form commonly prescribed in the United States, noting that the progestins used in the United States are of a lower dose and less strongly associated with breast cancer.[30]

Lacking any objective epidemiological evidence, Plaintiffs blow smoke, analogizing hormone therapy to cigarette smoking. No serious scientist, however, would think of comparing the relative risk of breast cancer from hormone therapy (1.24) with that of lung cancer from cigarette smoking (greater than 10.0 and as high as 30.0).[31]

CONCLUSION

Colditz Dep. at 69:9-12 (stating that, at a relative risk of approximately 1.2, use of hormone therapy is only a "weak risk factor" for breast cancer).

[29] Pl. Opp. at 11 (emphasis added).

[30] *See* Kjersti Bakken et al., *Hormone Replacement Therapy and Incidence of Hormone-Dependent Cancers in the Norwegian Women and Cancer Study*, International Journal on Cancer (2004) 112:130-34.

[31] *See* Sackett Rep. (App., Ex. 26) at 27. In sharp contrast to the lung cancer risk from smoking (10.0), the breast cancer risk from hormone therapy (1.24) is less than that from drinking a couple glasses of wine each night (2.0), *see* Klimberg Dep. at 252:22-254:3, and comparable to eating French fries as a kid (1.27), *see* Waldron Dep. 54:13-57:2.

Thus far, the Court has shown sage reluctance to "outrun[] [its] headlights in the field of medical science."[32] Heeding the classic admonition that "[l]aw lags science; it does not lead it,"[33] the Court should acknowledge that Drs. Klimberg and Waldron cannot identify, based on any objective evidence, the ***specific cause*** of Plaintiffs' breast cancers and, accordingly, exclude their expert testimony as to specific causation.

Respectfully submitted,

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[32] *In re Prempro Prods. Liab. Litig.*, 203 F.R.D. 555, 571 (E.D. Ark. 2005).

[33] *Rosen v. Ciba-Geigy Corp.*, 78 F.3d 316, 319 (7th Cir. 1996).

CERTIFICATE OF SERVICE

I hereby certify that on this 10th day of July 2006 a true and correct copy of the foregoing Reply in Support of Wyeth's Motion to Exclude Expert Testimony of Drs. Klimberg and Waldron as to Specific Causation was electronically filed with the Clerk of Court using the CM/ECF system and a true and correct copy was forwarded by e-mail and first-class mail, postage prepaid, to the parties listed below.

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